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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,555	11/12/2003	John W. Mickelson	PC27721A	6894

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PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
TUCKER, ZACHARY C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,555	MICKELSON, JOHN W.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *4,6-13 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

Response to Amendment

As requested in the correspondence from applicant's counsel, filed 21 June 2006 (hereinafter "present amendment"), which is in reply to the Office action mailed 22 November 2005 (hereinafter "previous Office action), claims 1 and 14-16 have been amended, and the abstract amended as well.

NOTE: The title of the application indicated on the correspondence from applicant's counsel is "Aryl fused heterocyclic compounds." The title of the instant application is "Pyrazine compounds as CRF modulators." It is requested that this matter be clarified.

Election/Restrictions

An election of species requirement is operative in the prosecution of the instant application. Since the present amendment does not overcome all of the rejections of record, based on prior art applied in the previous Office action, the search has not been expanded or continued. Prior art applied in the previous Office action still renders the presently amended claims unpatentable, as explained in the following paragraphs.

Because the elected Restriction Group (Group I) is not in condition for allowance, claims drawn to the nonelected inventions remain withdrawn from consideration at this time (claims 6-13 and 17-21). Comments pertaining to the rejoinder of claims 6-9 and 17-21 are provided in the section headed "Allowable Subject Matter," *infra*.

Applicant's elected species for examination, a compound wherein "X" is a substituted pyrrolidine ring, is not embraced by instant claim 4, which specifies "X" is a substituted piperidine ring. As such, claim 4 does not read on the elected species, and should have been withdrawn from consideration in the previous Office action. Since the

same prior art as was applied in rejections in the previous Office action is applied herein, albeit in a slightly different rejection (instead of being the basis for rejecting claims 1-3 under '102 and claim 5 under '103, all of claims 1-3, 5 and 14-16 are rejected under '103, based on that same prior art disclosure, in this Office action), claim 4 has not been searched, due to the nature of Markush practice, which is that the search is not broadened until the prior art applied in rejection of claims has been overcome.

Status of Claim Rejections - 35 USC § 112

In the previous Office action, claims 14-16 were rejected under the first paragraph of 35 U.S.C. 112, for failure to comply with the written description requirement. Compounds of the present invention are not inhibitors of corticotropin releasing factor (CRF) itself, as the claims specified prior to the present amendment; rather the compounds of the present invention are inhibitors of the CRF *receptor*. So, no description of the subject matter of claims 14-16 in their previously presented form was in the disclosure. As presently amended, claims 14-16 comply with the written description requirement of the first paragraph of this statute, and the rejection under 35 U.S.C. 112, first paragraph, of those claims, for failure to comply with that requirement, is hereby withdrawn.

In the previous Office action, claims 1-4 were rejected under the first paragraph of 35 U.S.C. 112, for lack of a disclosure enabling the production of prodrug forms of the compounds of Formula I.

In view of the present amendment to claim 1, deleting reference to prodrugs, the rejection of claims 1-4 for lack of enablement is hereby withdrawn. As noted

hereinabove, claim 4 should have been indicated as having been withdrawn, in the previous Office action.

Claims 1-4 and 14-16 were rejected under the second paragraph of 35 U.S.C. 112, for indefiniteness of the term "prodrug" in claim 1. Because the base claim from which claims 2-4 and 14-16 depend was found to be indefinite, all of the dependent claims were deemed indefinite because all incorporate the limitations of an indefinite base claim.

Because reference to prodrug forms of the Formula I compounds has been struck from claim 1, the rejection of claims 1-4 and 14-16 under the second paragraph of 35 U.S.C. 112 is hereby withdrawn. As noted hereinabove, claim 4 should have been indicated as having been withdrawn, in the previous Office action.

Claim 1 was found to be further indefinite because the term "modified monocyclic group" was deemed to be indefinite; not set forth as a proper Markush group and therefore ambiguous. In view of the present amendment to claim 1, wherein the "modified monocyclic group" is set forth as a proper Markush group, the rejection on that ground is withdrawn.

Claims 14-16 were found to be further indefinite because the conditions of the assay specified in those claims are not specified, thus the identity of the compounds according to those claims depended on an undefined variable.

In view of the present amendment to claims 14-16, the rejection of those claims on the ground of there being undefined assay conditions is withdrawn.

Status of Claim Rejections - 35 USC § 102

In the previous Office action, claims 1 and 2 were rejected under 35 U.S.C. 102(b) as being anticipated by US 4,081,542 (Lumma and Saari) or Lumma et al, *Journal of Medicinal Chemistry*, vol. 21(6), pages 536-542 (1978).

The compound disclosed by the two cited references, 5-phenyl-2-(1-piperazinyl)pyrazine, is no longer embraced by instant claims 1 and 2, because as presently amended, R_1 cannot be hydrogen.

In the previous Office action, claims 1-3 were rejected under 35 U.S.C. 102(e) as being anticipated by United States Patent Application Publication 2003/0018035 (Yoon et al).

The compounds disclosed by Yoon et al at page 18, 2-(2,4-dichlorophenyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-3,6-dimethylpyrazine and 2-(2,4-dimethoxyphenyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-3,6-dimethylpyrazine, are not embraced by instant claims 1-3, and were not before the present amendment. Neither R_1 nor R_2 is permitted to be methyl, and neither was this the case before the present amendment. The rejection of claims 1-3 as being anticipated by Yoon et al is hereby withdrawn in view of applicant's argument that it is improper.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

In the previous Office action, claim 5 was rejected under 35 U.S.C. 103(a) as being unpatentable over United States Patent Application Publication 2003/0018035 (Yoon et al).

Applicant's counsel argues that since the rejection statement provided in the previous Office action noted that "Yoon et al is applied against claim 5 under 35 U.S.C. 103(a) as set forth above in the rejection of claims 1-3 under 35 U.S.C. 102(e)," the rejection under 35 U.S.C. 103 necessarily falls if it can be shown that the anticipation rejection was improper. Rejection of claim 5 as being obvious over Yoon et al was not predicated on whether or not Yoon et al actually discloses any compound according to other claims under examination, so whether or not the rejection under 35 U.S.C. 102(e) was proper has no effect on whether the compounds of claim 5 are obvious in view of the reference.

The rejection is maintained, and is re-stated, so that the record is clear. Claims 1-3 and 14-16 are included now in the rejection based on Yoon et al.

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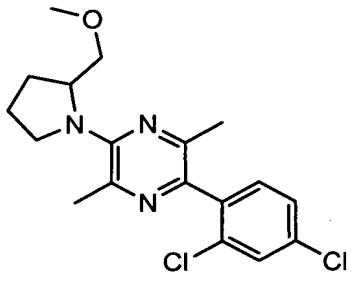
Claims 1-3, 5 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over United States Patent Application Publication 2003/0018035 (Yoon et al).

At the time the invention was made, compounds according to claims 1-3, 5 and 14-16 would have been obvious to the student of Yoon et al, of ordinary skill in the chemical arts.

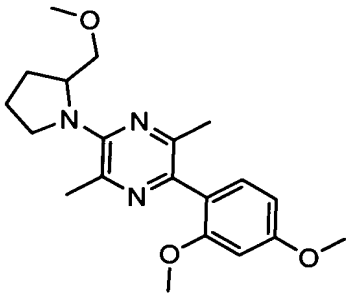
Yoon et al discloses substituted arylpyrazine CRF receptor antagonists.

Two such compounds disclosed in the Yoon et al publication are 2-(2,4-dichlorophenyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-3,6-dimethylpyrazine and 2-(2,4-dimethoxyphenyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-3,6-dimethylpyrazine, found at

page 18 (in Table I, examples 7 and 8), which are represented by the two following structure diagrams, respectively:



and



Neither of these two compounds is embraced by the instant claims, because R_1 and R_2 are not permitted to be methyl. The rest of the molecular structure of these two compounds correspond exactly with two of applicant's preferred species – wherein X is pyrrolidine substituted with $(CR_bR_b)_nZ$ – methoxymethyl; Ar is substituted aryl (dimethoxy or dichlorophenyl). So, the deficiency of Yoon et al with respect to instant claims 1-3 and 5 is that Yoon et al does not describe the synthesis of a compound embraced by those claims.

The two 2-(pyrrolidin-1-yl)-subsituted pyrazine compounds disclosed by Yoon et al are substituted with methyl at the 3- and 6-positions, but the majority of Yoon et al's compounds are 3,6-diethyl substituted, just as is the case with the species named in instant claim 5, and provided for in the definition of R_1 and R_2, in claims 1-3. Indeed, ethyl is expressly suggested as an identity for Yoon et al's substituent groups R_1 and R_3, as a "particularly preferred" substituent at those two positions. This is taught in sections [0088] – [0090], page 6.

Although Yoon et al does not explicitly disclose a compound embraced by the instant claims, compounds according to claims 1-3 wherein Ar is 2,4-dichlorophenyl or

2,4-dimethoxyphenyl, R_1 and R_2 are both ethyl, and X is 2-(methoxymethyl)pyrrolidin-1-yl are *expressly suggested* by Yoon et al and therefore are obvious in view thereof. The first and third named species in claim 5 correspond to these two obvious compounds suggested by Yoon et al.

The chemist of ordinary skill understands that in a disclosure such as Yoon et al, wherein a family of chemical compounds are described, and there are also set out some general teachings which apply to this family of compounds, that these general teachings are particularly applicable to the exemplified compounds. In the case of Yoon et al, it would have been obvious to make 3,6-diethyl homologs of 3,6-dimethyl compounds synthesized. Especially since *ethyl* is set forth as one of the particularly preferred R_1 and R_3 groups, which corresponds to R_1 and R_2 of the instant claims.

One of ordinary skill expects adjacent homologs, especially when those homologs are expressly suggested, to have similar pharmacological activity. The motivation to make the 3,6-diethyl homologs of Yoon et al's 3,6-dimethyl compounds noted above would have been to make antagonists of the human CRF receptor, for the treatment of depression and anxiety.

Claims 14-16 are included in this rejection based on Yoon et al, because compounds resulting from following the suggestion to introduce ethyl groups at the R_1 and R_3 positions in the generic formula taught by Yoon et al would be the first and third compounds as are specified in applicant's claim 5, ostensibly the most preferred compounds according to the present invention, which, according to the instant specification, have the properties (the specified IC_{50} in the receptor binding assay with IMR32 human neuroblastoma cells, which express corticotropin receptor). Page 24,

lines 25 and 26 of the instant specification teaches that the most preferred compounds according to the invention have an IC_{50} for binding with the corticotropin receptor in the assay referred to in parentheses in the previous sentence being below 10nM. The first and third compounds named in instant claim 5 are set forth as "particular compounds of the invention," which is taken to indicate the most particularly preferred compounds. Thus, these compounds have the properties specified in claims 14-16.

Abstract

In the previous Office action, the disclosure was objected to because the abstract was deemed to not be descriptive enough of the invention. In view of applicant's submission of an amended abstract, which is more descriptive of the invention, the objection is hereby withdrawn.

Allowable Subject Matter

Species of claim 5, excepting the first and third named compounds, are allowable. Yoon et al does not teach that the phenyl group corresponding to "Ar" in the compounds of the invention disclosed in that publication is preferably 2-chloro-4-methyl substituted, and at the same time having a 3,6-diethyl substitution about the pyrazine ring.

The closest prior art is Yoon et al, cited hereinabove, and US 6,964,965 (Corbett et al), which discloses a compound similar to those of the present invention. At column 23, lines 1-15 Corbett et al describes the compound 3,6-diethyl-3-(6-methoxy-2,3-dihydro-1H-inden-5-yl)-6-pyrollidin-1-yl-pyrazine, which corresponds to a compound of instant claim 1, except for the fact that no substituent is on the "modified monocyclic

group" of "X," which is required in claim 1. As such, Corbett et al does not disclose any compound according to the instant claims.

Another example of close prior art is CA 2 445 344 (Asaki et al), a Canadian patent application publication. Compounds similar to those of the present invention are described, but all of the exemplified compounds possess a substitution alkoxycarbonyl-alkyl-oxy-alkyl on what would correspond to "X" of the present claims in those compounds. The substituent on the "modified monocylic group" "X" is not permitted to be alkoxycarbonyl-alkyl-oxy-alkyl.

Should applicant's reply to this Office action overcome the rejection based on prior art, the search will be broadened and if art rendering any of the presently examined claims unpatentable is found, then the search will be stopped and the claims appropriately rejected. Upon allowance of Group I, which was elected in response to the Requirement for Restriction mailed 22 September 2005, claims of Group II will be eligible for rejoinder. Applicant's counsel is urged to limit the method-of-treatment claims to the treatment of depression, anxiety, and drug or alcohol withdrawal symptoms (and related conditions). Doing so will obviate a final rejection in which said claims are rejected under 35 U.S.C. 112, first paragraph.

Conclusion

This Office action is made non-final, because of the new rejection of claims 1-3 under 35 U.S.C. 103, which was not necessitated by amendment.

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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